

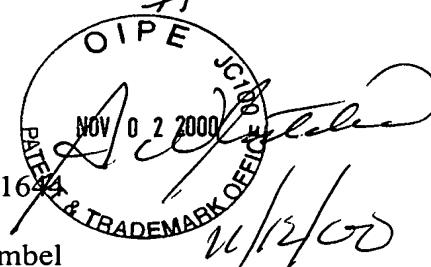
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Patent
Attorney NOV 07 2000 Docket No. 23522-0256

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE *#30*

In re Patent Application of)
Darrell R. ANDERSON et al.)
Application No. 08/746,361)
Filed: November 8, 1996)
For: IDENTIFICATION OF UNIQUE)
BINDING INTERACTIONS BETWEEN)
CERTAIN ANTIBODIES AND THE)
HUMAN B7.1 AND B7.2 CO-)
STIMULATORY ANTIGENS)

Group Art Unit: 164
Examiner: P. Gambel



REPLY AND AMENDMENTS PURSUANT TO 37 C.F.R. §§ 1.111 AND 1.115

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

In response to the outstanding Office Action [non-final rejection] mailed June 2, 2000, Applicants submit the following remarks. Reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow is respectfully requested.

Turning now to the Office Action, Applicants note that the Patent Office has concluded that the submitted figures are informal. Formal figures will be submitted upon indication that this application is otherwise in condition for allowance.

Applicants further note with appreciation that the previous § 102(e) rejection based on deBoer et al. (U.S. Patent 5,747,034) has been withdrawn in view of § 132 Declaration by Darrell Anderson under 37 C.F.R. § 1.132. However, claims 29-37 stand newly rejected based on the same deBoer reference and Linsley further in view of known procedures for

producing primatized antibodies, such as are disclosed in Newman et al. *Biotechnology* (1992). This rejection is respectfully but strenuously traversed.

Essentially, the position of the Examiner, is his assertion that the two patents, namely deBoer et al. and Linsley et al., would in combination teach an antibody having the specific binding properties of the present invention. This is traversed based on the following.

In particular, Applicants claim a novel and non-obvious monoclonal antibody, namely one which specifically binds to B7.1 antigen (CD80) and which inhibits the binding of B7.1 antigen to CD28, but which antibody does not inhibit the binding of B7.1 to CTLA-4. As discussed in the subject application, prior to the present invention, the only known antibodies which had been previously described having specificity to B7.1 antigen inhibited both the B7.1/CD28 antigen interaction and the B7.1 antigen/CTLA interaction. This is potentially disadvantageous, because the interaction of B7.1 antigen with CTLA-4 and CD28, delivers distinct signals to the T cell.

As previously argued, antibodies which possess the novel and non-obvious binding properties of the subject invention are advantageous in that they may possess distinct functional characteristics vis-à-vis previously known anti-B7.1 antibodies. Particularly, this is achieved because the subject antibodies do not affect the B7.1/CTLA-4 binding interaction.

Notwithstanding the fact that neither reference even remotely infers the existence of any antibodies possessing the novel and non-obvious binding properties of the subject invention, the Examiner asserts in the Office Action, that one of ordinary skill in the art would have been motivated to select anti-B7 antibodies with differential properties of binding

to CD28 and CTLA-4 with a “reasonable expectation of success.” However, the position of the Examiner is respectfully submitted to be improper.

An appropriate § 103 rejection, requires that the prior art must explicitly or implicitly provide motivation for a claimed invention, and furthermore there must be a reasonable expectation of success. Herein, neither of these prerequisites is satisfied. Indeed, Applicants have carefully reviewed both prior art references, however neither explicitly or implicitly teaches or suggests an antibody that meets the functional limitations particular to the claims. Rather, as previously argued. Linsley is limited in its teachings to the monoclonal antibody BB-1 which is specific to B7.1, which inhibits the interaction of B7.1 to CTLA-4 and CD28.

This is also true of the de Boer et al. antibodies as substantiated by the prior § 132 Declaration. By contrast, the monoclonal antibodies of the present invention do not inhibit the B7.1/CTLA-4 interaction. As explained above, this is a significant difference vis-à-vis the antibodies of Linsley et al. and de Boer et al. because the claimed antibodies, upon in vivo administration, should block binding of B7.1 of CD28 receptors, while allowing the negative signaling function of CTLA-4 to occur uninhibited. The preservation of such interaction should result in down regulation of the overall T cell activation response irrespective of the predominance of either TH1 or TH2 phenotypes. Based therein, the subject antibody should possess advantageous therapeutic properties, in particular for immunosuppression, for example in a treatment of autoimmune diseases, allergic disorders, prevention and treatment of graft v. host disease, bone marrow transplant and for the induction of host tolerance to donor specific alloantigens.

The Examiner seems to believe that because Linsley et al. and de Boer et al. provide a broad generic disclosure relating to the production of monoclonal antibodies specific to B7.1, that monoclonal antibodies possessing the claimed binding characteristics would have been obvious. However, in contrast to the Office Action, the prior art provides no indication that such an antibody could be obtained. Moreover, the prior art provides no incentive for producing such an antibody. In particular, it could not be reasonably predicted that such an antibody could be obtained, based on the fact that CTLA-4 and CD28 have a high degree of homology. Consequently, it could not have been reasonably expected that an antibody could be obtained which binds to B7.1 which inhibits the CD28 interaction, but which does not interfere with the CTLA-4 interaction. Rather, this result could only have been reasonably expected after obtaining an antibody possessing such a binding properties.

In this regard, Applicants respectively point out that obviousness is tested by what the combined teachings of the references would have suggested to one of ordinary skill in the art. For obviousness to be established, the Examiner must show that there is either a suggestion in the art to produce the claimed invention or compelling motivation based on sound scientific principles. *Ex parte Kranz* 19 USPQ 2d 1216, 1218 (PBAI 1991). Herein, the prior art completely fails to do so, since there is clearly no suggestion to produce antibodies possessing the novel and non-obvious binding properties of the claimed invention. At no point does either the Linsley et al. or the deBoer et al. patent teach or suggest the desirability of obtaining B7-specific antibodies which do not inhibit the interaction of B7 with CTLA-4. Nor is this an expected property, because of the fact that CTLA-4 and CD28 have a high degree of homology. Consequently, it would have been reasonably expected that an antibody

that binds to B7 and which inhibits the interaction with CD28 would also inhibit the interaction of this molecule with CTLA-4.

Moreover, even assuming for the sake of argument that such antibodies would have been *prima facie* obvious, the rejection should be withdrawn because of the unexpected nature of the claimed invention. Particularly, it has been now established that CTLA-4/B7 interactions act to down regulate immune responses. Accordingly, antibodies that fail to inhibit this interaction would be expected to be more efficient in inhibiting immune responses since the natural regulatory interaction of CTLA-4/B7 will not be disturbed. Therefore, the antibodies of the claimed invention are not functionally equivalent to those of the prior art. In this regard, the prior art provides no suggestion that antibodies specific to B7, could be derived having different functional characteristics than those of the prior art. Indeed, the only antibodies, known prior to the present invention, that specifically bind B7.1 inhibited both the CD28 and CTLA-4 interaction with B7.1.

Moreover, the obviousness rejection cannot be maintained, because there is no reasonable expectation, than an epitope even existed which would have allowed for the production of an antibody specific to B7.1, which inhibits the CD28 interaction, but which epitope does not involve the interaction of B7.1 with CTLA-4. Applicants' arguments are further substantiated by the fact that numerous antibodies specific to B7.1 antigen had been known prior to the present invention, however to Applicants' knowledge, none of such antibodies possess the novel and non-obvious binding properties of those of the present invention. Therefore, based on the foregoing, and absent and specific suggestion in either the deBoer or Linsley patents to produce an antibody possessing the claimed binding

characteristics, the § 103 rejection based on Linsley and deBoer should be withdrawn. Similarly, Newman does not compensate for the deficiencies of this rejection, since there would have been no reasonable expectation, that a primate antibody produced against B7.1 antigen, could be selected which possesses the novel and non-obvious binding properties of the claimed invention.

The only other outstanding issues are an obviousness type double patenting rejection based on allowed U.S. Serial 08/487,550 and related § 102(e) rejection. Upon an indication that this application is otherwise in condition for allowance, a Terminal Disclaimer will be submitted.

The § 102(e) rejection is respectfully traversed on the basis that the earlier application does not qualify as prior under 102(e) to the claimed invention. Indeed, Applicants are claiming antibodies which possess the same binding characteristics of those described in the earlier patent application. Particularly, the binding properties of the claimed antibodies, are inherent to those patented in the earlier application. Therefore, Applicants respectfully submit that the § 102(e) rejection is inappropriate because the claimed subject matter finds implicit support in the earlier application, which is relied upon for priority herein.

Based on the foregoing, this application is believed to be in condition for allowance. A notice to that effect is respectfully solicited. However, if any issues remain outstanding,

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the Examiner is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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